Testimony before the Subcommittee on Children's Health Committee on Environment and Public Works United States Senate

Statement for hearing entitled, "State of Research on Potential Environmental Health Factors with Autism and Related Neurodevelopment Disorders"

Statement of

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Chairman Klobuchar, Ranking Member Alexander, and distinguished members of the Subcommittee—I am pleased to appear before you today to present testimony on and the state of research efforts regarding potential environmental factors related to the development of autism and other neurodevelopmental disorders. My name is Linda Birnbaum; I am the Director of the National Institute of Environmental Health Sciences (NIEHS) of the National Institutes of Health and the National Toxicology Program (NTP) within the Department of Health and Human Services (HHS).

Scientists have made tremendous progress in understanding how the brain and nervous system grow and function. Research supported by NIEHS has clearly shown that it is not just genetics, but the complicated interplay of both genes and the environment that determines the risk of many neurodevelopmental disorders. We now have new information on the role that early environmental exposures may play in the development of a broad spectrum of childhood and adult disorders, including autism, attention deficit hyperactivity disorder (ADHD), and learning disorders. NIEHS-supported researchers are beginning to unravel some of the mysteries of how neurodevelopment may be impaired by looking at the possible effects of timing and concentration of environmental and lifestyle exposures (e.g., diet or smoking), including low-dose exposures before birth and during early childhood, on the vulnerability of the developing brain.

Environment and Autism

Autism spectrum disorder (ASD) is a neurodevelopmental condition whose rates have increased significantly in U.S. children in the past several years.[1] Much research is now focused on this disorder, and NIEHS has significantly increased its funding in this area in recent years. NIEHS spent $9.3M on autism in FY 2009, of which $4.4M was from our regular appropriation and $4.9M was from funds provided under the American Recovery and Reinvestment Act (ARRA). I am an active member of the Interagency Autism Coordinating Committee (IACC), a group of Federal agencies and public members (parents and people living with autism) that works to plan and coordinate a research agenda that simultaneously meets the goals of science and reflects the input and concerns of the autism community.

NIEHS's two largest efforts on autism are the Childhood Autism Risks from Genes and the Environment, or CHARGE study, and the Early Autism Risk Longitudinal Investigation, or EARLI study. In the EARLI study, researchers at the Drexel University School of Public Health are enrolling mothers who have a child with autism and who are pregnant again. One of the largest studies of its kind, this longitudinal study will follow 1,000 mothers during their pregnancy and their new babies through age three to identify prenatal, neonatal, and early postnatal exposures that may influence their risk of developing autism. The EARLI study is based on the theory that detection of autism risk factors will be enhanced by prospective data collection during the pregnancy period, and that a cohort of pregnancies at higher risk for autism (because the mothers have a previous child with autism) provides an efficient strategy for detecting such risk factors. This study is part of the trans-NIH Autism Centers of Excellence (ACE) Program and is jointly funded by NIEHS and three other NIH Institutes (the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the

[1] http://www.cdc.gov/ncbddd/autism/data.html

National Institute of Mental Health (NIMH), and the National Institute of Neurological Disorders and Stroke (NINDS)) and the advocacy group Autism Speaks.

The CHARGE study is coordinated by the Children's Center at the University of California at Davis and co-funded by NIEHS and EPA. Launched in 2003, it is the first large-scale human population case-control study of children with autism. Researchers are looking at a wide range of environmental exposures and their effects on early development in more than 1,600 California children. Three groups of children are enrolled in the CHARGE study: children with autism, children with developmental delay who do not have autism, and children from the general population. All of the children are evaluated for a broad array of exposures and susceptibilities with the goal of better understanding the causes and contributing factors for autism or developmental delay.

Heavy metals are one of the classes of exposure being investigated in the CHARGE study. A recent paper discussed study findings that demonstrated that current blood levels of mercury do not differ in children with autism versus controls when adjustments for fish consumption are made.[2] Additional analyses of mercury are underway to more directly address its role in development of autism and to better understand the mechanism of action. Perhaps the most interesting new findings from the CHARGE study relate immune system alterations in children to the development of autism. These findings point to the need for further study on the interface of the immune and nervous systems in autism etiology. [3 4 5 6]

ARRA provided a key opportunity to increase NIH support for autism research. NIEHS joined four other NIH institutes (the National Institute of Mental Health, , the National Institute of Neurological Disorders and Stroke, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, and the National Institute on Deafness and Other Communication Disorders) in a broad initiative soliciting applications to address the IACC strategic plan, including objectives related to potential environmental contributors to autism. Four ARRA grants were awarded by NIEHS through this initiative. These grants capitalize on existing studies, including the CDC Study to Explore Early Development (SEED), CHARGE, the Finnish National Birth cohort, and the Early Markers of Autism Risk (EMAR) study. ARRA funding is being provided:

- To examine whether air pollution due to traffic, a common environmental exposure, increases risk for ASD. This study will also look at genes that process pollutants in the

[2] Hertz-Picciotto I, Green PG, Delwiche L, Hansen R, Walker C, Pessah IN. Blood mercury concentrations in CHARGE study children with and without autism. Environ Health Perspect 2010;118:161-166.
[3] Gregg JP, Lit L, Baron CA, Hertz-Picciotto I, Walker W, Davis RA, Croen LA, Ozonoff S, Hansen R, Pessah IN, Sharp FR. Gene expression changes in children with autism. Genomics. 2008 Jan;91(1):22-9.
[4] Heuer L, Ashwood P, Schauer J, Goines P, Krakowiak P, Hertz-Picciotto I, Hansen R, Croen LA, Pessah IN, Van de Water J. Reduced levels of immunoglobulin in children with autism correlates with behavioral symptoms. Autism Res 2008 Oct;1(5):275-283.
[5] Enstrom AM, Onore CE, Van de Water JA, Ashwood P. Differential monocyte responses to TLR ligands in children with autism spectrum disorders. Brain Behav Immun 2010 Jan;24(1):64-71.
[6] Ashwood P, Enstrom A, Krakowiak P, Hertz-Picciotto I, Hansen RL, Croen LA, Ozonoff S, Pessah IN, Van de Water J. Decreased transforming growth factor beta1 in autism: a potential link between immune dysregulation and impairment in clinical behavioral outcomes. J Neuroimmunol. 2008 Nov 15;204(1-2):149-153.

body to determine if they are different in children with and without autism, and to see if they interact with air pollution to increase autism risk.[7]

- To determine whether polyfluoroalkyl compounds, or PFCs, which are widespread and persistent industrial pollutants that may interfere with the actions of hormones, are found at higher levels in samples from newborns who are later diagnosed with autism as compared to samples from newborns that develop normally.[8]

- To analyze several types of chemicals—including pyrethroid pesticides, flame retardants (such as PBDEs), and plasticizers (such as bisphenol A and phthalates)—that are being found in greater amounts in the environment but have not previously been looked at in relation to their potential effects on autism. This study will expand an existing autism study by adding collection and analysis of household dust and a food frequency questionnaire to determine exposures.[9]

- To identify genes whose effects on ASD may vary depending on the mother's exposures during pregnancy (including smoking and alcohol use, medication, and infection) using data obtained on 500 autism cases and controls through SEED, a large epidemiologic investigation of autism.[10]

NIEHS also provided ARRA supplements to autism investigators, including a supplement to hire additional outreach coordinators for the EARLI study, new personnel to speed up analysis and publication of pending CHARGE study findings, and support for home visits to CHARGE families to collect dust samples for analysis of additional exposures.

Neurodevelopment and Cognition

The work we fund on autism spectrum disorders is an important part of our overall investment in children's neurological development, which totaled over $29 million in FY2009 (almost $18M from the regular NIEHS appropriation plus $11.5 million in ARRA funds.) With this investment, NIEHS supports a wide range of studies covering the role of environmental effects on children's neurological development and behavior. While the research mentioned below is not specific for disorders related to autism spectrum disorders, the research will provide us with a better general understanding of neurological development and behavior in children.
Development of the nervous system begins in the womb and extends throughout childhood. During these periods of rapid development, the brain is vulnerable to some environmental exposures that may have the potential to disrupt the chemical signals that organize development. Even small changes in the timing of critical developmental events can potentially have major consequences for brain structure and function. Thus, even brief adverse exposures at these vulnerable stages can have lasting effects on adult brain function .[11] [12] We refer to "windows of

[7] 1 R21 ES019002-01 -- Investigating Gene-Environment Interaction in Autism: Air Pollution – McConnell, Robert S. (CA)
[8] 1 R01 ES019003-01 -- Prenatal Exposure to Polyfluoroalkyl Compounds in the EMA Study – Croen, Lisa A. (CA)
[9] 1 R01 ES015359-03S2 – The CHARGE Study—Autism Risk from Genetics and the Environment – Hertz-Picciotto, Irva (CA)
[10] 1 R01 ES019001-01 -- Genome-wide Environment Interaction Study for Autism: The SEED study – Fallin, Danielle (contact); Newschaffer, Craig (MD)

[11] Gilbert & Epel, Ecological Developmental Biology, Sinauer Press, 2009
[12] Dale Purves et al. 2008 Neuroscience, Fourth Edition, Sinauer Press, 2008 (see Unit IV, The Changing Brain)

susceptibility" to mean the life stage at which the brain is exposed, during which different agents can affect the brain in specific and deleterious ways. For example, the dose of lead that is neurotoxic to an infant is much less than the dose that would be neurotoxic for an adult, so infancy in this case is a "window of susceptibility."[13] [14] [15] Our full research portfolio on environmental impacts on brain and nervous system development gives us a full scientific context that may help us interpret results from our autism studies.

Learning disabilities are on the rise in the United States[16], and we now have a significant body of information on how exposure to certain environmental agents can affect children's intelligence quotients (IQs). For example, scientific literature attests to the effects of lead exposure in early life on IQ. [17] [18] The more recent studies of lead have detected cognitive effects even below the CDC action level of 10 micrograms of lead per deciliter of blood.[19] CDC's National Health and Nutrition Examination Survey (NHANES) from 1999-2000 estimated that 434,000 children ages 1-5 years had blood lead levels greater than or equal to 10 micrograms per deciliter.[20] Mercury also has been shown in multiple studies to be a developmental neurotoxicant. And studies in Bangladesh have found that concentrations of arsenic[21] and manganese[22] in drinking water are associated in a dose-dependent fashion with decreases in intelligence.

We are finding that metals are not the only toxic agents to affect IQ, learning, and memory. A study published last year from Columbia University showed that a mother's exposure to urban air pollutants known as polycyclic aromatic hydrocarbons (PAHs) can adversely affect a child's IQ. PAHs are released into the air from the burning of coal, diesel, oil, gas, and other organic substances such as tobacco. In urban areas, motor vehicles are a major source of PAHs. The researchers found that children in New York City who were exposed *in utero* to high levels of PAHs had full-scale and verbal IQ scores that were 4.31 and 4.67 points lower than those of less exposed children.[23]

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[13] (ATSDR). 2007. Toxicological profile for Lead. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service)." (http://www.atsdr.cdc.gov/ToxProfiles/tp13-c3.pdf

[14] Jett DA, Kuhlmann AC, Farmer SJ, Guilarte TR. Age-dependent effects of developmental lead exposure on performance in the Morris water maze. Pharmacol Biochem Behav. 1997 May-Jun;57(1-2):271-9

[15] Sanders T, Liu Y, Buchner V, Tchounwou PB. Neurotoxic effects and biomarkers of lead exposure: a review. Rev Environ Health. 2009 Jan-Mar;24(1):15-45

[16] http://www.cdc.gov/nchs/data/series/sr_10/Sr10_237.pdf

[17] Baghurst PA, McMichael AJ, Wigg NR, et al. Environmental exposure to lead and children's intelligence at the age of seven years: the Port Pirie Cohort Study. N Engl J Med 1992;327:1279-1284.

[18] Bellinger D, Dietrich KN. Low-level lead exposure and cognitive function in children. Pediatr Ann 1994;23:600-605.

[19] Rogan WJ, Ware JH. 2003. Exposure to lead in children – how low is low enough? N Engl J Med 2003;348:1515-1516.

[20] http://www.cdc.gov/mmwr/preview/mmwrhtml/ss5210a1.htm

[21]Wasserman, G.A., X. Liu, F. Parves, H. Ahsan, P. Factor-Litvak, A. van Geen, V. Slavkovich, N.J. LoIacono, Z. Cheng, I. Hussain, H. Momataj, and J.H. Graziano. September 2004. Water Arsenic Exposure and Children's Intellectual Function in Araihazar, Bangladesh. *Environmental Health Perspectives* 112(13):1329-1333.

[22]Wasserman, G.A., X. Liu, F. Parvez, H. Ahsan, D. Levy, P. Factor-Litvak, J. Kline, A. van Geen, V. Slavkovich, N.J. LoIacono, Z. Cheng, Y. Zheng, J.H. Graziano. 2005. Water Manganese Exposure and Children's Intellectual Function in Araihazar, Bangladesh. *Environmental Health Perspectives*. 114(1):124-129.

[23] Perrera FP, Zhigang L, Whyatt R, Hoepner L, Wang S, Camann D, Rauh V. Prenatal airborne polycyclic aromatic hydrocarbon exposure and child IQ at age 5 years. Pediatrics 2009;124(2):e195-202.

In another report, Columbia University researchers examined the association of prenatal exposure to a common flame retardant called PBDE (polybrominated diphenyl ether) with neurodevelopment. Two hundred and ten cord blood specimens were analyzed for selected PBDE chemical varieties and neurodevelopmental effects in the children were assessed at ages 1, 2, 3, 4, and 6 years. The findings demonstrated that adverse effects on neurodevelopment were related to cord blood PBDE concentrations.[24] [25] These investigators are currently leading a longitudinal cohort study initiated following the 9/11 attacks that includes 329 participants who were pregnant at the time of the event and delivered babies in one of three hospitals in lower Manhattan, to look at potential effects of prenatal toxic air exposures on neurodevelopment.

In a very different community, NIEHS funded researchers have been conducting a long-term, ongoing study of effects on growth, intellectual function, and ADHD of Inuit children exposed pre-and post-natally to polychlorinated biphenyls (PCBs), methylmercury, lead, and docosahexaenoic acid (DHA), which is the omega-3 fatty acid that is critically important for growth and development of neurons and retinal cells. The study, which was designed to be culturally appropriate to ensure accurate findings (cognitive tests were translated into the native Inuit language and adjusted for cultural understanding), has produced several unpublished findings concerning the transmission of pollutants in breastfeeding and the benefits of DHA during pregnancy. Although these findings will be published in the fall, specifics cannot be shared at this time, since our researchers agreed at the beginning of the study to review their findings first with the Nunavik Nutrition and Health Committee and the Municipal Councils of the three major Inuit villages where data collection took place. This study also is looking at transmission of methylmercury through breastfeeding; child body burdens from birth through 11 years of age; and the potential beneficial effects for children of increased intake of DHA by mothers, particularly during the third trimester of pregnancy.

Neurobehavioral Outcomes: ADHD

In addition to effects on learning, NIEHS scientists have found that early environmental exposure to some of these same chemicals, such as lead and mercury, can affect behavior. Early lead exposure, for example, has been associated with aggressive behavior at different age levels from toddler to adolescent.[26] Investigators at Cincinnati Children's Hospital, one of NIEHS's Centers for Children's Environmental Health and Disease Prevention, co-funded by NIEHS and the Environmental Protection Agency, are conducting research on childhood lead and prenatal tobacco exposure and the potential connection to development of ADHD in children. These investigators have shown that such exposures, when linked with certain genes for susceptibility, may act as precursors to development of ADHD. These investigators also found that childhood

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[24]Herbstman JB, Sjodin A, Kurzon M, Lederman SA, Jones RS, Rauh V, Needham LL, Tang D, Niedzwiecki M, Wang RI, Perera F. Prenatal exposure to PBDEs and neurodevelopment. Environ Health Perspect. 2010 May;118(5):712-9.

[25] The plasma samples were analyzed for the following PBDE congeners (by International Union of Pure and Applied Chemistry numbers): 2,2,2',4,4'-tetraBDE (BDE-47); 2,2',3,4,4'-pentaBDE (BDE-85); 2,2',4,4',5-pentaBDE (BDE-99); 2,2',4,4',6-pentaBDE (BDE-100); 2,2',4,4',5,5'-hexaBDE (BDE-153); 2,2',4,4',5,6'-hexaBDE (BDE-154); 2,2',3,4,4',5',6-heptaBDE (BDE-183); and 2,2',4,4',5,5'-hexaBB (BB-153).

[26] Hornung RW, Lanphear BP, Dietrich KN. Age of greatest susceptibility to childhood lead exposure: a new statistical approach. Environ Health Perspect. 2009 Aug;117(8):1309-12

exposure to lead and prenatal exposure to tobacco are risk factors for ADHD, accounting for about one out of three cases of ADHD in U.S. children.[27]

A recent report in NIEHS's journal *Environmental Health Perspectives* (*EHP*) looked at the association of prenatal phthalate exposure with behavior and executive function[28] at 4-9 years of age in the Mt. Sinai Children's Environmental Health Study cohort. The study found that increased concentrations of certain byproducts of phthalate exposure in the urine of mothers during pregnancy were associated with poorer scores on a variety of measures of aggression, as well as conduct problems, attention problems, and depression in their children.[29] Another *EHP* publication just released online, by NIEHS-funded investigators at Boston University School of Public Health, measured exposures to four types of polyfluoralkyl compounds (PFCs) and their relation to ADHD, using data from almost 600 children taken from the National Health and Nutrition Examination Survey (NHANES) from HHS's Centers for Disease Control and Prevention (CDC). PFCs are widely used in consumer products and have been shown in animal data to be potential neurotoxicants. This study has shown increased risk of ADHD in children with higher serum PFC concentrations.[30]

NIEHS-funded researchers at Harvard University have recently published compelling findings showing associations between prenatal exposure to methylmercury, in some cases combined with PCBs, and memory and learning impairment, as well as adverse behavior and decreased impulse control in adolescents.[31] This work has provided the basis for a pilot project within a Children's Environmental Health and Disease Prevention Research Formative Center that NIEHS recently funded, which will focus on the relationship of exposure to bisphenol A and phthalates with neurobehavioral outcomes in adolescents.

Pesticides, both agricultural and home use, are also being investigated in relation to ADHD. The center at Harvard University has just released a report showing an association between exposure to organophosphate pesticides and development of ADHD.[32] Although we do not yet know the mechanism underlying these associations, these researchers are actively investigating these questions.

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[27] Froehlich TE, Lanphear BP, Auinger P, Hornung R, Epstein JN, Braun J, Kahn RS. Association of tobacco and lead exposures with attention-deficit/hyperactivity disorder. Pediatrics 2009 Dec;124(6):e1054-1063

[28] The term executive function describes a set of cognitive abilities that control and regulate other abilities and behaviors. Executive functions are necessary for goal-directed behavior. They include the ability to initiate and stop actions, to monitor and change behavior as needed, and to plan future behavior when faced with novel tasks and situations.

[29] Engel SM, Miodovnik A, Canfield RL, Zhu C, Silva MJ, Calafat AM, Wolff MS. Prenatal phthalate exposure is associated with childhood behavior and executive functioning. Environ Health Perspect. 2010 Apr;118(4):565-71.

[30] Hoffman K, Webster TF, Weisskopf MG, Weinberg J, Vieira VM, 2010 Exposure to Polyfluoroalkyl Chemicals and Attention Deficit Hyperactivity Disorder in U.S. Children Aged 12-15 Years. Environ Health Perspect doi:10.1289/ehp.1001898 Link to article

[31] Sagiv SK, Thurston SW, Bellinger DC, Tolbert PE, Altshul LM, Korrick SA. Prenatal organochlorine exposure and behaviors associated with Attention Deficit Hyperactivity Disorder in schoolaged children. Am J Epidemiol 2010;171:593-601.

[32] Bouchard MF, Bellinger DC, Wright RO, Weisskopf MG. Attention-deficit/hyperactivity disorder and urinary metabolites of organophosphate pesticides. Pediatrics 2010;125(6):e1270-e1277.

In summary, environmental influences on brain development, behavior, and other neurological outcomes of public health concern are a rapidly growing area of environmental health sciences and a high priority for NIEHS. We believe that our investments will help to advance our understanding of these conditions, and provide critically needed information to drive prevention and treatment options for children. Thank you for the opportunity to testify; I would be very happy to answer your questions.